Chapter 25
Global Governance of Anti-microbial Resistance: A Legal and Regulatory Toolkit

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Abstract Recognizing that antimicrobial resistance (AMR) poses a serious threat to global public health, the World Health Organization (WHO) has adopted a Global Action Plan (GAP) at the May 2015 World Health Assembly. Underscoring that systematic misuse and overuse of drugs in human medicine and food production is a global public health concern, the GAP-AMR urges concerted efforts across governments and private sectors, including pharmaceutical industry, medical professionals, agricultural industry, among others. The GAP has a threefold aim: (1) to ensure a continuous use of effective and safe medicines for treatment and prevention of infectious diseases; (2) to encourage a responsible use of medicines; and (3) to engage countries to develop their national actions on AMR in keeping with the recommendations. While the GAP is a necessary step to enable multilateral actions, it must be supported by effective governance in order to realize the proposed aims.

This chapter has a threefold purpose: (1) To identify regulatory principles embedded in key WHO documents relating to AMR and the GAP-AMR; (2) To consider the legal and regulatory actions or interventions that countries could use to strengthen their regulatory lever for AMR containment; and (3) To highlight the crucial role of the regulatory lever in enabling other levers under a whole-of-system approach. Effective AMR containment requires a clearer understanding of how the regulatory lever could be implemented or enabled within health systems, as well as how it underscores and interacts with other levers within a whole-of-system approach.

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E. Jamrozik, M. Selgelid (eds.), *Ethics and Drug Resistance: Collective Responsibility for Global Public Health*, Public Health Ethics Analysis 5,
https://doi.org/10.1007/978-3-030-27874-8_25

Keywords Global action plan · Governance · Regulation · Law/legal · Collective action · Stewardship

25.1 Introduction

Antimicrobial resistance (AMR) is widely recognized as a public health threat, responsible for 700,000 deaths worldwide. If the spread of antimicrobial resistance is left unaddressed, it could lead to 10 million additional annual deaths by 2050, according to an estimation by the World Bank. Facilitated by inappropriate uses of medicines to control the spread of infection for human and animal health, antimicrobial resistance also poses long term threat to human development. The United Nations (UN) Secretary-General Ban Ki-Moon describes AMR as a "fundamental threat" to human development at a high-level UN meeting on drug-resistant bacteria (United Nations News Centre 2016). Likewise, recognizing the gravity of antimicrobial resistance on global health, the then Director-General for the World Health Organization (WHO) Margaret Chan characterizes the rise of AMR as a "slow-motion tsunami" (Leatherby 2017). Without an effective global containment strategy, the World Bank warns, the economic impact of AMR makes it unlikely for the world to reach the sustainable development goals set for 2030 (World Bank 2017).

Scientists have long known that microbes can become resistant to medicine. Alexander Fleming, the Nobel laureate for the discovery of penicillin, cautioned the world in his 1945 Nobel acceptance speech of the impending public health crisis (Fleming 1945, at p. 93): "… there is the danger that the ignorant man may easily under dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." Since the 1950s the WHO has identified AMR as a global threat, but little progress has been made in improving access to antimicrobials and maintaining their appropriate consumption and effectiveness. Likewise, limited innovation in antimicrobials further compounds the challenge. For these reasons, a broad range of microorganisms have become more resistant to antimicrobials in all parts of the world. An emerging concern is AMR for diseases which affect low and middle income countries (LMICs) disproportionately, such as tuberculosis (TB), malaria and HIV (See Chaps. 2–4). Furthermore, with extensively drug-resistant to tuberculosis now identified in 105 countries, it further raises concerns of a future TB epidemic where limited treatment options are available.

Even though the direct consequences of AMR on human health were beginning to be scientifically well-understood several decades ago, international efforts to address this problem did not begin till the late 1990s and 2000s. The WHO played a key role in catalysing international actions on the issue. It convened a series of consultative groups and expert workshop to assess, evaluate, and develop a series of recommendation for effective containment interventions to garner international attention. This work culminated in the report *WHO Global Strategy for Containment*

of Antimicrobial Resistance (World Health Organization 2001). Since this strategy was published, AMR has been discussed at several World Health Assembly meetings, resulting in the adoption of several resolutions such as WHA60.16 concerning the rational use of medicine and WHA62.15 on prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. At the 2015 World Health Assembly, member states endorsed a *Global Action Plan on Antimicrobial Resistance* (GAP-AMR; World Health Organization 2015a) – which calls for an effective One Health approach – and which was later endorsed through resolutions by the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE). In the same year, AMR was recognized as a threat to the world's sustainability and human development at the UN level. In a landmark UN resolution guiding the global development plan for the next 15 years entitled *Transforming our world: the 2030 Agenda for Sustainable Development* (United Nations 2015), AMR is mentioned but not explicitly set out as a Sustainable Development Goals (SDGs) target. Most recently, the G20 summit reaffirmed the commitment to combat antimicrobial resistance (G20 Leaders' Declaration 2017).

These commitments, both within and outside of the high-level political setting of UN organs, underscore the growing political interest in AMR. Two distinct but interrelated factors explain the recent high-level political attention. First, national governments have a strong self-interest in mitigating the negative impacts of AMR on public health: the estimated economic cost for failing to address the issue would be £66 trillion in lost productivity to the global economy (Public Health England 2015). Second, AMR transcends national borders and exposes a global vulnerability which necessitates collective action at the international level. The shared vulnerability underpinning AMR was recently acknowledged by Tedros Adhanom, the WHO Director-General, in his address to the G20 summit. Urging the world to act, he underscored the interdependence of the world, noting "… vulnerability for one is vulnerability for all of us" (World Health Organization 2017a). German Chancellor Angela Merkel echoed this concern, depicting AMR as akin to a global health security issue of global collective responsibility (Scheuber 2017).

This chapter has a threefold purpose: (1) To identify regulatory principles embedded in key WHO documents relating to AMR and the GAP-AMR; (2) To consider the legal and regulatory actions or interventions that countries could use to strengthen their regulatory lever for AMR containment; and (3) To highlight the crucial role of the regulatory lever in enabling other levers under a whole-of-system approach. In the section that follows, we consider how the WHO and other international bodies have systematically framed this global health issue as a collective action problem; initially by setting out the WHO GAP-AMR. But subsequently, it was quickly recognised that a global plan would not be self-enabling and therefore a global framework has since been proposed by the UN to facilitate implementation by all member states. We set out what we consider to be the core principles that are embedded in the GAP-AMR and the global framework built around it. We then consider the regulatory lever that member states need to establish and apply in order for these principles to effect change at the national level.

25.2 The WHO and AMR

25.2.1 Collective Action Problem

Ilona Kickbusch and David Gleicher (World Health Organization 2012a, b) define global health as health issues which transcend national boundaries and governments and call for actions on the global forces and global flows that determine the health of people. As microbes are capable of penetrating national borders, national efforts are contingent upon, and vulnerable to external actions and forces. It is widely recognised that a collective response is necessary to mitigate the negative consequences of AMR. As no country is capable of addressing the issue without some degree of mutual reliance on others to mount an effective response against AMR, the interdependency makes AMR containment a collective action problem.

Some scholars go further and argue that the containment of AMR is a public good: the benefits from effective containment are enjoyed by all and there is no rivalry in consumption (Smith and Coast 2002). If this is correct, it could present a free rider problem: individual states lack incentive to take the necessary actions and instead, rely on others to act. Arguably, the free rider problem can be addressed through international law (Wernli et al. 2011; Review on Antimicrobial Resistance 2014). Steven Hoffman and Asha Behdinan (2016), Reinl (2016), Susan Rogers Van Katwyk et al. (2016), Christine Årdal et al. (2016), and Asha Behdinan et al. (2015), for instance, argue that countries can be encouraged to act if international law embeds incentives. While many international institutions are involved in addressing the threat posed by AMR, as a starting point, we focus the discussion on the WHO, particularly for its instrumental role in developing the GAP-AMR.

25.2.2 Global Action Plan

Recognizing that systematic misuse and overuse of antimicrobial drugs in human medicine and food production puts every nation at risk, the overarching goal of the GAP-AMR is thus to ensure that the world is able to "treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them" (World Health Organization 2015a, b, at p. 8). To achieve this goal, the GAP-AMR requires concurrent actions at the national and international levels. While the GAP-AMR is not technically binding, it seeks to harmonise practices across countries while affording regulatory flexibility. To assure policy coherence at the national and international levels, the GAP-AMR provides five objectives to guide and align national and international policy actions: (1) to improve awareness and understanding of AMR through effective communication, education and training; (2) to strengthen the knowledge and evidence base through surveillance and research; (3) to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; (4) to optimize the

use of antimicrobial medicines in human and animal health; and (5) to develop the economic case for sustainable investment that takes account of the needs of all countries, and increases investment in new medicines, diagnostic tools, vaccines and other interventions. Member states are urged to have national action plans that are aligned with the GAP-AMR within 2 years of the endorsement of the action plan by the World Health Assembly.

Moreover, because excessive human and animal use of antibiotics in multiple settings will have health, economic and security implications beyond national borders, the GAP-AMR embraces a *One Health* approach towards AMR. Defined as a collaborative, multi-sectoral and trans-disciplinary, the *One Health* approach recognizes interconnection between people, animals, plants and the shared environment. This approach calls for sectorial coordination involving human and veterinary medicine, agriculture, finance, environment, and consumers to optimal health outcomes. At the level of international health, horizontal coordination of different UN agencies occurs through the WHO. As the specialized public health agency within the UN agency, the WHO is charged with organizing international responses to shared health challenges, and this responsibility includes acting as "the directing and coordinating authority on international health work" (World Health Organization n. d.). The WHO works with the Strategic and Technical Advisory Group on AMR at the FAO and OIE to develop a framework for monitoring and evaluation of member states' national action plans. Likewise, the FAO, OIE and World Bank are encouraged to put in place and implement action plans in their respective fields. Notably, the regulatory functions bestowed on the WHO are broader in scope than any other international agency in the UN orbit.

As of 2017, more than one third of WHO member states have completed their national action plans on AMR, and a further 62 are in the process of doing so. These national action plans provide a basis for an assessment of the resource needs at national and international levels. The WHO is tasked with publishing biennial progress report on countries' progress in implementing their national action plans. The progress report will also include an assessment of progress made by the FAO, OIE and WHO.

25.2.3 Limitations of the Global Action Plan

To be sure, the GAP-AMR provides a good starting point, but the plan lacks concrete goals to compel action. Moreover, the WHO alone cannot be expected to solve the global AMR crisis. For instance, preserving antimicrobial medicines will require a global agreement as to what constitutes 'appropriate use'. Likewise, new financing mechanisms will be needed to incentivise global innovation in antimicrobial medicines. Thus, in the same resolution that endorsed the global action plan, the World Health Assembly (2015a, b) requested the Director-General to develop a global development and stewardship framework to support GAP-AMR in combating AMR. Specifically, the Health Assembly requires the Director-General to (World Health Assembly 2015a, b, Request 7):

> develop, in consultation with Member States and relevant partners, options for establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and in line with the global action plan on antimicrobial resistance.

The global framework will build on the GAP-AMR, but with specific focuses on preservation of antimicrobial medicines and development of new antimicrobial medicines, diagnostic tools, vaccines and other interventions. According to a report issued by the FAO, OIE and WHO (Food and Agriculture Organization 2017, at p. 4), a global development and stewardship framework would have a threefold goal:

1. Stewardship: Preserving antimicrobial medicines through a stewardship framework covering control, distribution and appropriate use;
2. Research & Development: Developing of new health technologies for preventing and controlling antimicrobial resistance; and
3. Access: Promoting affordable access to existing and new antimicrobial medicines and diagnostic tools.

This framework further encapsulates key principles that have been expounded in earlier initiatives of the WHO. For the purposes of this chapter, we highlight three principles that are of especial pertinence to laws and regulations on pharmaceuticals, which are discussed in the section that follows (for a broader ethical discussion on AMR, see Haire, Chap. 3, this volume; Cheah et al., Chap. 4, this volume). Not necessarily in order of priority, these principles are:

1. Rational and responsible use of antimicrobials

At a practical level, the WHO defines rational use of medicines as patients receiving medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community (World Health Organization 1985). This definition extends to the use of antimicrobials, where for instance, irrational use occurs when patients are prescribed and/or take antibiotics (intended to treat bacterial infection) when in fact they have a viral infection. As a matter of public policy, responsible use of antimicrobials is set out as a governing principle that should underpin national governments' efforts to curb AMR. This principle requires governments to ensure that existing activities, capabilities and resources of health system are aligned to ensure patients receive the right dosage of antimicrobials at the right time, use them appropriately and benefit from the usage (World Health Organization 2012a, b).

2. Equitable access to, and appropriate use of, existing and new antimicrobial medicines.

The GAP-AMR recognizes that all countries should have a national action plan on antimicrobial resistance that includes an assessment of resource needs. Moreover, recognizing the need to optimise the use of antimicrobial medicines in human and

animal health, the WHO has updated its model list of essential medicine which categories antibiotics into three groups: access, watch and reserve. The access group include antibiotics (considered to have low resistance potential) recommended as first or second choice treatment options for common infections. This group of antibiotics should be widely available at an affordable cost and of assured quality. The watch group of antibiotics are those generally considered as to have higher resistance potential but are recommended as for first or second choice treatment for limited number of indicators. The reserve group consists of 'last-resort' options, or tailored to highly specific patients and setting, and when other alternatives have already failed. International efforts are required in monitoring, reporting the uses of reserve antibiotics to preserve their effectiveness (World Health Organization 2017b, c).

3. Transparency: Data Sharing, Collection and Evaluation

Data sharing, collection and evaluation have been emphasised in order to promote transparency and collaboration. A report by the WHO Secretariat on antimicrobial resistance sets these responsibilities out concisely as (World Health Organization 2015a, at p. 11): "Publishing biennial progress reports, including an assessment of countries and organizations that have plans in place, their progress in implementation, and the effectiveness of action at regional and global levels; and including an assessment of progress made by the FAO, OIE and WHO in implementing actions undertaken within the organizations' tripartite collaboration will also be included in these reports."

Significantly, the call for a global development and stewardship framework was later reiterated at a high-level meeting on antimicrobial resistance at the UN level in 2016 (United Nations 2016). It was the only fourth time that the UN General Assembly convened a high-level meeting on a health issue. Previous meetings – HIV/AIDS, Ebola and non-communicable diseases – catalysed and mobilized political actions at the international level. The UN Political Declaration on antimicrobial resistance was adopted by all 193 member states, signalling a global commitment to combat antimicrobial resistance.

In the discussion so far, we have considered the framing of AMR as a collective action problem the WHO and other international organisations. We have also briefly set out how the GAP-AMR and an enabling global framework have been constructed in response to this problem. More importantly, we have attempted to identify key principles that are embedded in the GAP-AMR, and in respect of which the global framework seeks to give expression to. For ease of reference, we refer to them generally as regulatory principles, because member states need to incorporate them – through laws and regulations – within their health systems. These laws and regulations collectively constitute a regulatory lever that will, at a basic level, enable member states to design, implement and manage policies (particularly pharmaceutical oriented ones) toward responsible use and good stewardship of antimicrobials. These laws and regulations are considered in the next section of the chapter. We then explain why a sound regulatory lever within a whole-of-system approach is

critical to enable other levers (financial and information ones in particular) to operate effectively in meeting global AMR objectives.

25.3 Regulatory Leverage for Responsible Use and Good Stewardship of Antimicrobials

The prevalence of AMR is heavily influenced by the way that antimicrobials are consumed. It is now well established that overuse and underuse of antibiotics can lead to resistance (Jamrozik and Selgelid, Chap. 1, this volume). Even so, improper or imprudent use of antibiotics is deeply entrenched within health systems. In order for all member states of the WHO to meet their moral and political commitments set out under the GAP-AMR, it is critical for health systems to be strengthened on all fronts. Clearly the challenge of AMR is a complex one because it is influenced by many different factors and conditions. At the level of health systems, the relational dynamics between prescribers (or suppliers) of antibiotics and patients (or consumers), financial incentives, systemic commitments and characteristics, and the regulatory environment, are arguably the key contributors to AMR. For the purposes of this chapter, we focus on the role of regulation (broadly applied to refer to both legislative and regulatory actions) and examine how it could be used to support the containment of AMR. Many countries do not have a substantially clear and systematic legal and regulatory framework that is specifically directed at AMR (for example, Singh 2017). At a fundamental level, a clear regulatory position on responsible antimicrobial use that simultaneously prioritises effective antimicrobial stewardship is a pre-requisite to a coordinated response in policy decisions and actions across different domains within a health system. In addition, a variety of regulatory interventions should be considered to enable, as well as promote, the use of structural (delivery arrangement), information and financial levers to encourage appropriate use and stewardship of antimicrobials. It is further important for the regulatory environment to be sufficiently open in allowing a combination of top-down and bottom-up actions within a whole-of-system approach.

Policy discussions on effective stewardship of pharmaceuticals in health systems as a response to the problem of AMR predate the GAP-AMR. In a WHO report (Bigdeli et al. 2014) published ahead of the 2015 World Health Assembly, four main policy objectives with respect to medicines (and antimicrobials) in health systems have been identified as: (1) widely available high-quality medicinal products; (2) equitable access; (3) appropriate and safe use; and (4) affordability. Different policy actions and conditions are matched to each of the four policy objectives in the following manner (Bigdeli et al. 2014, at p. 45):

1. Ensuring availability of quality generic and innovative products:
    - Monitoring product quality;
    - Prequalifying supplies and products;

- Negotiating prices, quality, volume, and supply-chain security;
- Promoting fair competition;
- Engaging in risk sharing agreements;
- Establishing patient access programmes;

2. Improving Equitable Access:

- Understanding utilization profiles;
- Assessing of care seeking behaviour and barriers to care;
- Expanding provider networks;
- Targeting policies and programmes to improve access for vulnerable populations;

3. Encouraging Appropriate Use:

- Implementing and updating standard treatment guidelines;
- Matching essential medicines and reimbursement lists to standard treatment guidelines;
- Assessing provider performance;
- Managing care comprehensively;
- Implementing and monitoring policies to encourage clinically appropriate and cost-effective use;

4. Keeping cost affordable:

- Monitoring routine medicines expenditures by therapeutic area;
- Evaluating health technologies and budget impact;
- Assessing household medicines expenditure;
- Implementing and monitoring policies and programmes to reduce waste and inappropriate use.

Not surprisingly, these policy objectives are closely aligned with what we have identified to be regulatory principles that underscore the GAP-AMR. For instance, rational and responsible use, equitable access and transparency are all necessary conditions to ensure the availability of quality antimicrobials within a health system. However, these policy objectives and their attending actions and conditions inevitably compete in many ways. Price pressures could limit investment in governance infrastructure, where such limitations are typically manifested in weak regulatory capacity, information imbalance, lack of coordination among different stakeholders and perverse incentives whereby irresponsible use is directly supported by direct financial gain. Over time, these practices not only strain health systems by increasing needless consumption, cost and inefficiencies, but also accentuate the global threat of AMR. Within the paradigm of value-based practice, the problem of AMR highlights the urgent need to shift current low-value practices to high-value ones (Porter 2010; Elshaug et al. 2017). A low-value practice is an intervention where evidence suggests that it confers no or very little benefit (to a patient for instance). It also depicts any practice where risk of harm exceeds probable benefit, or where added costs of the intervention do not provide proportional added benefits.

In contrast, a high-value practice is one where evidence suggests it confers benefit on the intervention subject, or probability of benefit exceeds probable harm, or where the added costs of the intervention provide proportional added benefits relative to alternatives. For instance, overprescribing that is incentivised, among other factors, by increased revenue for healthcare providers through greater pharmaceutical sales is a low-value practice that continues to be sustained in many health systems.

While it is beyond the scope of this chapter to address comprehensively the value implications of inappropriate use and poor stewardship of antimicrobials, our intent is to make explicit an implicit understanding that responding to the AMR challenge could be closely linked to addressing many on-going concerns relating to quality of care (World Health Organization 2016). The role and impact of regulation on quality of care have been a longstanding concern among a variety of scholars in different quarters. With limited exception however (notably in the work on refining the working definitions for substandard and falsified medical products (World Health Organization 2017c)), there has not been as much focus on the regulatory lever within health systems on containment of AMR as compared to the financial lever, for example. We hope to address this deficiency by proposing different tools and conditions that could make-up or compose the regulatory lever in relation to each of the four policy objectives identified by the WHO, as well as propose what we consider to be a sufficient open and responsive regulatory environment that could constructively resolve tensions by focusing on higher-value practice when these objectives come into conflict.

25.3.1 Ensuring Quality

A sufficiently robust and up-to-date legal and regulatory framework is necessary to control the quality, safety and efficacy of pharmaceuticals, including antimicrobials. Substandard or degraded antimicrobials, where dosage may be lower or less effective, contribute to therapeutic failure and could thereby encourage the development of drug-resistant strain of pathogens. Similarly, counterfeit antimicrobials could have an adverse effect if the active ingredients include other types of antibiotics (and/or other drugs). In order for such a legal and regulatory framework to be robust, regulatory actions must include accreditation, audit and inspection for the purposes of controlling quality and assessing the safety and efficacy of antimicrobials. For instance, health systems that manufacture antimicrobials must have a legal and regulatory framework to ensure that good manufacturing standards and practices are adhered to. It is not enough to only specify these requirements, but it is just as important for regulatory mechanisms to be in place that can effectively detect deficiencies or deviations from prescribed standards and practices.

Appropriate laws and regulations are also needed to legitimise, implement and sustain policies and programmes that are directed at rational and appropriate antimicrobial use. These policies and programmes generally relate to disease surveillance

and management, and standard treatment guidelines. More recently, various measures have been introduced to incentivise the use of high value care through pay-for-performance programmes. These programmes reward healthcare providers for achieving quality, efficiency and "value" by increasing accessibility and appropriate use of drugs that are of proven efficacy. However, evidence of the effectiveness of such programmes are mixed in high-income countries and extremely limited in LMICs. From a regulatory standpoint, pay-for-performance programmes are not self-enabling everywhere but are likewise dependent on a supportive regulatory environment. Broadly speaking, appropriate legal or regulatory principles should be in place to ensure fair bargain, safety and (where appropriate) fair compensation, monitoring and data sharing.

In summary, the following legal and regulatory interventions should be considered in advancing the policy goal of ensuring availability of quality (generic and innovative) antimicrobials:

- Laws and regulations on standards and practices that ensure quality level is achieved (e.g. good manufacturing standards and practices);
- Legally sanctioned practices for monitoring product quality and prequalifying supplies and products (e.g. through licensing, accreditation, audit and inspection);
- Law and regulations that promote fair competition or that enable regulatory action to be taken against anti-competitive practices;
- Legally entrenching disease surveillance and management programmes; and
- Set out legal and regulatory baseline and principles for risk sharing agreements and patient access programmes.

25.3.2 Improving Prescribing and Dispensing

In many LMICs, antimicrobials are sold over-the-counter without a prescription or otherwise dispensed by individuals who lack professional training or authority. Even where there may be laws or regulations that proscribe such practices, they may be poorly or inadequately enforced (Singh 2017; World Health Organization 2015b). For instance, accreditation and professional licensing may not specifically target adherence to standard treatment guidelines. Consequently, the failure to adhere to guidance on responsible antimicrobial prescription would not render the healthcare provider professionally accountable or otherwise legally empower a professional body to take remedial action. Responsible prescribing and dispensing practices could also be hampered by weak healthcare infrastructure, expectations of patients and perverse financial incentives. Access to rapid or reliable diagnostic tests may be limited in a low resource health system. This could in turn encourage healthcare providers to veer towards prescribing an antibiotic in order to ensure that the prospect of a bacterial infection is addressed even if there is no reliable diagnosis to that effect. Such a conservative approach could even be a cost effective response (in the short term) if the cost of the antibiotic is lower than to order a laboratory test to

validate a diagnosis (World Health Organization 2015b). For this and other reasons, providers may feel obligated to prescribe – while patients may feel entitled to use – antimicrobials, as a quick treatment option. Patients may not be aware of what appropriate use of antimicrobials means, particularly where duration of medical consultation is limited, and could consider themselves to have received substandard care if they have not been prescribed an antibiotic. At a systemic level, financial incentives may encourage overprescribing of antimicrobials. Where pharmaceutical sales generate revenue for healthcare providers and institutions, there would be a perverse financial incentive to overprescribe. Such a practice may be exacerbated where pharmaceutical companies themselves enter into profit-sharing arrangements with these providers or institutions. Additionally, it is currently impossible to determine the extent that antimicrobials are appropriately prescribed and consumed as there is a lack of reliable data across all health systems.

Laws and regulations are necessary to prohibit over-the-counter sale of antimicrobials while ensuring that patients continue to have access through appropriately trained and qualified healthcare professionals. In addition, requiring an appropriate amount of information to be indicated on packaging and to be shared as part of responsible prescribing practice could be given regulatory force. On the former, such a requirement could be taken up as a regulatory measure to ensure high-value or quality use of antimicrobials, particularly where full treatment courses are to be dispensed. Healthcare providers, institutions and professional associations have a crucial role to play in robust guideline development and implementation processes, filling evidence gaps with research, developing high-value practices, and leading or participating in efforts to shift from low-value to high-value practices. In many health systems, these stakeholders do not have sufficient or appropriate legal standing to contribute constructively to policy measure that are directed at improving prescribing and dispensing practices (Singh 2017; World Health Organization 2015b). As noted earlier, professional associations that have an interest in ensuring that standard treatment guidelines are observed by their members may not have any regulatory authority to monitor and improve such practices. Where professional organisations have the capability and motivation to improve professional practices, appropriate laws and regulations could be facilitative of this in a manner that is transparent and accountable. The challenge of perverse financial incentives is perhaps more difficult to surmount, particularly if the health system concerned is committed to particular structural arrangements or values. Legal or regulatory intervention could then be a platform for evaluation, discussion and change. For instance, legal and regulatory changes introduced by South Korea in 2000 to prohibit doctors from dispensing drugs have reduced inappropriate antibiotic prescribing (Kwon 2003; Park et al. 2005).

In summary, the following legal and regulatory interventions could be considered to improve prescribing and dispensing of antimicrobials:

- Prohibit over-the-counter sale of antimicrobials;
- Lend regulatory weight to standard treatment guidelines;

- Empower healthcare institutions and professional associations to improve prescribing and (where applicable) dispensing practices through means that include assessing provider performance;
- Introduce regulation to ensure that care is managed comprehensively;
- Laws and regulations that support implementing and monitoring policies to encourage clinically appropriate and cost-effective use of antimicrobials; and
- Evaluate, remove or manage perverse financial incentives through appropriate laws and regulations.

25.3.3 Ensuring Appropriate, Affordable and Equitable Access

The policy goals of ensuring appropriate, affordable and equitable access to pharmaceuticals (including antimicrobials) are aligned with the WHO's global health initiative on universal health coverage (UHC), broadly directed at promoting access for all to appropriate health services at affordable cost (World Health Assembly Resolution 2005; World Health Organization 2010a, b). Much discussion on UHC has focused on expanding populations covered by national payment systems, although comparatively little information exists on what pharmaceutical are provided, whether they meet the healthcare needs of the population, and how health systems manage pharmaceuticals so that patients receive high-value services at costs that households and systems can afford. When the types of pharmaceuticals provided do not meet population needs, risk protection is inadequate and this does not prevent household impoverishment (Yip and Hsiao 2009; Parry 2012; Wagner et al. 2008).

The economic burden of pharmaceuticals on households is high: they account for nearly half of household healthcare expenditures in 12 Asia-Pacific countries (Wagner and Ross-Degnan 2009) and for all healthcare expenses in four out of 10 households in 22 low- and 17 middle-income countries (Wagner et al. 2011). Pharmaceuticals also constitute a major source of inefficiencies in health systems. Of the ten leading sources of inefficiency in health systems identified in the 2010 World Health Report, pharmaceuticals account for the top three (World Health Organization 2010a). Underuse of generic products, use of substandard and counterfeit medicines, and inappropriate use of medicines waste scarce resources in systems. The World Health Organization estimates that more than half of all medicines globally are prescribed, dispensed, or sold inappropriately (World Health Organization 2009). For instance, overuse of antibiotics to treat acute respiratory tract infections wastes resources and leads to use of higher cost second and third line antibiotics for drug resistant infections. In many LMICs, access to a qualified healthcare professional may cost patients more time and money when compared with inappropriately or illegally obtaining antibiotics over-the-counter or from an unauthorised vendor. To promote appropriate and affordable access, national antibiotics policies and standard treatment guidelines must be supported by essential medicines lists or formularies that encourage rational and responsible use of

antimicrobials. In addition, appropriate laws and regulations must be in place to ensure that the antimicrobial supply chain is secure in terms of their procurement, storage and sale (World Health Organization 2015b). These requirements extend to importation requirements and quality inspections for health systems that do not manufacture antimicrobials.

The use of antimicrobials in animals for food production or other purposes will also need to be carefully monitored and regulated. Whereas laws and regulations have conventionally been domain specific particularly in keeping regulations relating to humans distinct from nonhuman animals, the *One Health* approach endorsed in the GAP-AMR highlights the need for a more comprehensive and coordinated approach across the food, veterinary and health sectors. Many countries have yet to establish a regulatory mechanism to enforce requirements for appropriate use of antimicrobials in animals. In addition, there is inadequate infrastructure for monitoring and controlling the development of resistant pathogens in animals, their vertical transmission from one animal species to another, as well as zoonotic transmissions to humans.

Above all, WHO policy documents and guidance (2010a, 2014, 2016, 2017a) have consistently emphasised the importance of promoting equity through greater stakeholder engagement and prioritising the worst off (or otherwise the most vulnerable) in a given society. This could be especially important for decentralised health systems, where inequalities across regions may be great (see also Reid, Chap. 16, this volume). A related concern is that public awareness of appropriate antimicrobial use remains low in most, if not all, health systems. Even within healthcare institutions, infrastructure and human resources may not be adequately equipped to implement and manage infection prevention and control programmes. Equitable access as devised through paradigms such as "accountability for reasonableness" (Daniels and Sabin 2002) is arguably more likely to enable and encourage relevant stakeholders – particularly the broader community – to be interested and proactively involved in national antibiotics policies and related infection prevention and control programmes. As we shall elaborate on below, an equitable regulatory lever is crucial in support bottom-up approaches to promoting high-value use of antimicrobials (Tang et al. 2016).

In summary, the following legal and regulatory interventions could be considered to ensure appropriate, affordable and equitable access to antimicrobials:

- Introducing laws and regulations that implement and sustain infection prevention and control programmes, including appropriate surveillance mechanisms, to understand utilisation profiles, assess care seeking behaviour and barriers to care, and improve access for vulnerable populations;
- Regulation could be the basis of public awareness campaigns and continuing education for stakeholders;
- Laws and regulations may be needed to support monitoring routine medicines expenditures by therapeutic area, evaluating health technologies and budget impact, and assessing household medicines expenditure;
- Implementing and monitoring policies and programmes to reduce waste and inappropriate use through appropriate regulations;

- Requiring appropriate stakeholders' involvement or contribution through regulation; and
- Reduce the use of antibiotics as growth promoters in animals through laws and regulations.

25.4 Regulatory Lever Within a Whole-of-System Approach

In our discussion above, we have considered the different types of legal and regulatory actions or tools that could constitute the regulatory lever, taking into account pharmaceutical policy goals and the GAP-AMR regulatory principles. We have also noted that the regulatory lever is but one of other levers that are available to policymakers, two of such levers being financial and information. In this section, we broadly explain why the regulatory lever underscores the effectiveness of these two other levers within a "whole-of-system" approach that is directed at AMR containment. By this approach, we adopt the WHO's emphasis that focus should not be limited to a particular component of a health system – broadly defined to mean "all organizations, people and actions whose primary intent is to promote, restore and maintain health"- but to recognise that different systemic components are interrelated and interact in ways that may be anticipated or unanticipated (World Health Organization 2010a; b, at p. 19).

25.4.1 Financial Lever

The financial lever could be thought of as being constituted by financial schemes that include budget controls, tax and incentive arrangements, and also the policies and actions of healthcare purchasers or payers, particularly social insurers (Bigdeli et al. 2014). Ideally, financing schemes should be designed to support decision-making through provision of information on demographic characteristics, healthcare needs and utilisation patterns of its users, and also of healthcare providers – particularly prescribing patterns and related costs. Implementers of financial schemes exert a degree of financial control over patients and healthcare providers in terms of what they pay for, and could shape patient demand through both financial and educational means. Additionally, financial incentives should encourage cost-effective prevention and care, while financial commitments should be directed at meeting infrastructural requirement, such as surveillance mechanisms that allow the use of international and local data on disease burden and utilisation patterns to signal potential inappropriate use patterns. In reality, financial interventions, like expenditure-focused policy instruments, tend to lack specificity and often have unintended effects. For instance, a cap on funding does not necessarily encourage clinically appropriate use or otherwise reduce wasteful spending as a result of over-treatment.

Within a whole-of-system approach, the financial lever should be applied together with the regulatory lever to support the establishment of a sound information environment, by making available evidence-based clinical guidelines and economic assessments that include health technology assessment and budget impact. As we have noted above, this is crucial in overcoming the current challenge that too little information on monitoring and evaluation activities is available, primarily due to lack of mechanisms in many health systems to monitor antimicrobial prescription and use. While some information is available on how medicines are financed in these health systems, there is little information to reliably determine equitable access and appropriate use.

25.4.2 Information Lever

The information lever of many health systems is disproportionately focused on price rather than on appropriate use and good stewardship. There is a need to review, revise and develop information systems to collect information that will enable policy-makers to target policies that improve prescribing practices, carry out audits and conduct education programmes. Such a system should also be able combine information from different parts of the healthcare system. Regular samples of paper-based facility prescribing and dispensing records can provide information on utilization to inform policy decisions (World Health Organization 2015b).

Policies that ensure appropriate use of antibiotics in a manner that is effective, safe, equitable and efficient depend on the availability of information including population demographics, disease epidemiology, treatment approaches, and political and economic environments. Health systems will need to be capable of generating routine, up-to-date information about the type of antibiotics that are needed by patients, which antibiotics are being used and how they are used across different patient populations within the health system, who prescribed them, whether they are clinically appropriate (such as in addressing the disease burden faced by the population) and the cost spent. Without such information, it will be difficult to determine if quality of care is provided. Ideally, information systems should capture details on the antibiotics use and expenditure, along with quality of care (such as the percentage of primary care patients receiving antibiotics), and details of misuse. However, these details are usually not captured by data collection systems. For instance, where providers are paid through bundled-payment arrangements (whether case or episode-based), the information system may not be designed to capture data on the type and amount of antibiotics prescribed, since payment does not depend on such information. As we have noted above, appropriate laws and regulations could help bring about changes to information systems that prioritises AMR containment.

Constant monitoring, feedback and evaluation are important to ensure that levers continue to achieve desired goals. Crucially, member states will need to ensure that the whole-of-system approach to AMR containment could be implemented bottom-up and top-down (Elshaug et al. 2017). Bottom-up actions require stakeholders who are not in any formal positions of authority to change practices that are within their

sphere of influence. Such stakeholders could be patients, clinicians, cooperatives and agricultural producers (see Schwenkenbecher, Chap. 23, this volume and Oakley, Chap.8 in this volume). In contrast, top-down actions have wider impact and the drivers of change typically include governments, professional bodies and third party payers. The use of the regulatory lever, along with other levers, should enable as well as facilitate a combination of both bottom-up and top-down actions to improve policies and practices relating to antibiotics access, use and stewardship.

25.5 Conclusion

In this chapter, we have considered how AMR containment has become a collective action problem, perhaps most comprehensively mapped out in the GAP-AMR. While the GAP-AMR itself lacks legal or regulatory force, there are at least three regulatory principles that could be drawn from it. These regulatory principles in turn require countries to adopt a variety of legal and regulatory actions or interventions that may be necessary to strengthen their regulatory lever for AMR containment. We have attempted to explicate these legal and regulatory actions in terms of four pharmaceutical policy objectives that have been articulated in a number of WHO documents and initiatives. Finally, we highlighted the crucial role of the regulatory lever in implementing the GAP-AMR, and also in enabling other levers under a whole-of-system approach.

Policies on AMR in health systems need to be responsive to shifting contexts and goals. Such adaptations must be informed by the best available evidence of what works, for whom, how and why in a given situation. In addition, routine monitoring and periodic evaluations of the impacts are necessary, and they are further crucial to ensuring quality, appropriate use and good stewardship of antimicrobials. The regulatory lever could and arguably should be applied to introduce, guide, scale-up, adapt, adjust or terminate policies on AMR containment. While it is not disputed that the regulatory lever is generally recognised to be important, there has been relatively little attention as to what it means in terms of laws and regulations that could be directed at AMR containment. If the GAP-AMR is to be effectively enabled, this lacuna that we have highlighted will require greater attention.

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